Adverse effects of intrapleural instillation of tissue plasminogen activator in a horse

Adverse effects of intrapleural instillation of tissue plasminogen activator in a horse; suspected re-expansion pulmonary oedema

B.C. McGorum*, C.H. Stratford, J.A. Keen and R.S. Pirie

Royal Dick School of Veterinary Studies and Roslin Institute, University of Edinburgh, Easter Bush Campus, Midlothian EH25 9RG, United Kingdom

**Corresponding author email: bruce.mcgorum@ed.ac.uk*

Keywords: horse; pulmonary oedema; tissue plasminogen activator; pleuropneumonia

Summary

This case report describes a 5-year-old pregnant Warmblood mare which was being treated for fibrinous bacterial pleuropneumonia. Since initial attempts to drain and lavage both pleural cavities were ineffective due to the presence of extensive intrapleural fibrin loculations, recombinant human tissue plasminogen activator (tPA) was instilled into both pleural cavities, to promote fibrinolysis and improve drainage. Within 1-2 h of instilling tPA, the horse became distressed, with increasing dyspnoea, tachycardia, pleurodynia and hypoxaemia. At 4 h post tPA instillation, diffuse bilateral pulmonary oedema was evidenced by the onset of widespread audible inspiratory crackles and ultrasonographic ring-down artefacts. Ultrasonography demonstrated that tPA had induced pleural fibrinolysis, thereby removing the restrictive effects of pleural adhesions on lung motion and facilitating lung re-expansion. Re-expansion pulmonary oedema **(**RPE) was suspected, although an adverse drug reaction could not be excluded. The complication resolved with nasal oxygen supplementation, and administration of frusemide, meloxicam, morphine and hydroxyethyl starch. Subsequent repetition of

intrapleural tPA instillation and thoracic drainage had no apparent adverse effect. The mare was discharged from the hospital and subsequently foaled successfully. The pathogenesis, diagnosis and management of RPE is reviewed.

Introduction

RPE is a potentially fatal iatrogenic complication of rapid lung re-expansion following thoracocentesis for the treatment of pneumothorax or pleural effusion. RPE has an incidence of 0.9-32.5% and a mortality rate of 1.2-20% in human patients undergoing thoracic drainage (Mahfood *et al.* 1988; Kim *et al.* 2009; Taira *et al.* 2014). While RPE is proposed as one of the mechanisms contributing to equine post-anaesthetic pulmonary oedema (Ball and Trim 1996; Kaartinen *et al.* 2010), it has not been reported following equine pleural drainage. Given that human RPE may be under-diagnosed when mild or asymptomatic, and when post procedure imaging is not performed (Feller-Kopman *et al.* 2007; Taira *et al.* 2014), RPE may also be under-diagnosed in horses. This report describes the successful treatment of a case of suspected RPE in a horse which developed following intrapleural tPA instillation for management of fibrinous pleuropneumonia. Brief details of this case were included in a review of 25 horses which had received tPA for the treatment of fibrinous pleuropneumonia (Tomlinson *et al.*, 2015).

Case details

Case history

A 5-year-old, 567 kg body weight, 4 month-pregnant, Warmblood mare presented to Dick Vet Equine Hospital with fibrinous bacterial pleuropneumonia following long distance transportation 6 days previously.

Clinical examination

The mare had pyrexia (39.3^{o}C), tachycardia (65 beats/min), tachypnea (32 breaths/min), shallow breathing pattern with increased inspiratory effort, elevated jugular pulse and a grade 1-2/6 left sided early systolic murmur presumed to be a flow murmur. Normal breath sounds were audible over both dorsal hemithoraces but were absent over both ventral hemithoraces. No crackles were audible.

Diagnosis and treatment

Ultrasonography revealed bilateral pleural effusion, marked organising fibrin pleural adhesions and loculations and collapse of ventral lung regions (Supplementary Video File 1). Pleural fluid extended to a level approximately 56% up an imaginary transect from the ventral to dorsal pleural reflections, at a level immediately caudal to the forelimbs, bilaterally. Lung motion during the breath cycle was severely restricted. Ultrasonographic ring-down artefacts were not evident at this stage. *Streptococcus zooepidemicus* and *Chryseomonas indologenes* were cultured from pleural fluid and tracheal aspirate, respectively. Cefquinome, gentamicin, metronidazole, flunixin, meloxicam and intravenous crystalloid fluid therapy were administered at various time points during the hospitalisation period. The mare's clinical parameters remained fairly stable for the first 3 days of hospitalisation. Attempted pleural drainage and lavage (5-10 L Hartmann's solution) via bilateral indwelling thoracic drains daily for 3 days was ineffective because of extensive fibrin loculations. Total net volumes of pleural fluid obtained over the first 3 days were only 13 L and 6 L from the left and right pleural cavities, respectively. Immediately after the third attempt to drain the pleural cavities, to promote fibrinolysis and facilitate more effective drainage, recombinant human tissue plasminogen activator (tPA; 12.5 mg in 1L 0.9% NaCl) was instilled into each pleural cavity, and the drains clamped, with a view to repeating thoracic drainage and lavage 12-24 h later.

However, within 1-2 h following this procedure, the mare became agitated and increasingly dyspnoeic. Breathing and heart rates increased to 60/min and 110/min, respectively. Breathing pattern changed from shallow to deep, with increased inspiratory and expiratory effort, and externally audible inspiratory and expiratory 'puffing'. At this stage, thoracic auscultation revealed increased audibility of breath sounds over the dorsal hemithoraces, but no adventitious sounds. Subjectively there was increased evidence of pleurodynia, manifested as increased reluctance to move, increased bruxism and occasional expiratory grunting. There were marked generalised fine muscle tremors. Cardiac rhythm, pulse strength, mucous membrane colour and capillary refill time remained unremarkable. Vaginal endoscopic examination was unremarkable. Ventilation perfusion mismatching and alveolar hyperventilation were evidenced by decreases in PaO_2 (84 to 66 mmHg), SaO_2 (96 to 92%) and $PaCO_2$ (48 to 30 mmHg). Supplemental intranasal O_2 was supplied at 10-15 L/min. Given the apparent increase in pleurodynia, morphine (120 mg IV) and meloxicam (140 mg IV) were administered; this improved demeanour only marginally and did not prevent the continuing increase in heart and breathing rates. Clinical parameters continued to deteriorate and at 4 h post tPA instillation diffuse bilateral pulmonary oedema was evidenced by the onset of widespread and increasingly audible end inspiratory crackles and diffuse ultrasonographic ring-down artefacts present over the entire lungfield (Supplementary Video File 2). At this stage, ultrasonography demonstrated that tPA had rapidly induced partial pleural fibrinolysis, with the fibrin loculations being partially replaced by freely moving fluid containing hyperechoic foci. It was apparent that pleural fibrinolysis had reduced the restrictive effects of pleural adhesions on lung motion, thereby increasing lung motion during the breath cycle, and facilitating re-expansion of the previously collapsed ventral lung. Ultrasonography also revealed a clinically insignificant small volume pneumothorax and absence of pericardial effusion and haemothorax. RPE was suspected, although an adverse drug reaction could not be eliminated.

Treatment of suspected RPE

Intranasal oxygen supplementation was continued. Frusemide (500 mg IV) and hydroxyethyl starch (6% 130/0.4 in 0.9% saline; 1 L/h IV) were administered, and intravenous crystalloids discontinued. Clinical parameters continued to deteriorate for 6-8 h following tPA instillation, before stabilising and thereafter improving gradually. Clinical parameters and arterial blood gas concentrations had returned to baseline (i.e. pre-tPa instillation) levels by 12-24 h. Ultrasonographic examination at 18 h post tPA instillation demonstrated resolution of ring-down artefacts, lysis of fibrin loculations, increased lung motion and re-expansion of ventral lung regions (Supplementary Video File 3). Intranasal O_2 was discontinued after 24 h. Further thoracocentesis, pleural lavage and intrapleural tPA instillation was delayed for 24 h. Thoracic drainage performed 48 h after tPA instillation yielded 10 and 5 L pleural fluid containing numerous clumps of fibrin from left and right hemithoraces, respectively (Figures 1 and 2). Subsequent thoracocentesis (n=11) and bilateral intrapleural tPA instillation (n=3) had no apparent adverse effects, yielding a total of 22.5 L and 25 L, from left and right hemithoraces, respectively. Thoracic drains were removed after 13 and 19 days. Thereafter the mare made an uneventful recovery, foaled successfully and was alive 8 months after hospital discharge.

Discussion

RPE is a potentially fatal iatrogenic complication of rapid lung re-expansion following thoracocentesis for the treatment of pneumothorax or pleural effusion. While the pathophysiology of RPE remains poorly understood, it is likely multifactorial, with pulmonary vascular injury and increased pulmonary capillary permeability having key contributing roles (Genofre *et al.* 2003; Sherman 2003; Feller-Kopman *et al.* 2007; Sohara 2008). Risk factors for RPE in some studies include severity and duration of lung collapse, rapidity of lung re-expansion, use of high suction pressures for thoracocentesis and the concomitant presence of

pneumothorax and pleural effusion (Mahfood *et al.* 1988; Taira *et al.* 2014). In this case, the suspected RPE was clearly not a consequence of rapid drainage of pleural fluid, because fibrin loculations prevented effective drainage, and only small volumes of pleural fluid had been obtained. In contrast, we hypothesise that RPE developed because of rapid re-expansion of chronically collapsed lung as a result of rapid breakdown of restrictive fibrin adhesions and loculations following intrapleural fibrinolysis. Consistent with this possibility, ultrasonography indicated that pleural fibrinolysis had indeed rapidly (within 4 h) reduced the restrictive effects of pleural adhesions on lung motion, thereby facilitating lung re-expansion of the previously collapsed ventral lung regions. RPE appears to be an uncommon adverse consequence of this treatment, since this horse was the only one of 25 tPA treated horses that developed suspected RPE (Tomlinson *et al.* 2015). The authors are unaware of reports of RPE following intrapleural tPA instillation in human patients.

There is no definitive diagnostic test for RPE. In human patients, RPE is suspected whenever there is sudden respiratory or haemodynamic deterioration following pleural drainage of air or fluid (Mahfood *et al.* 1988). The mare in this report met clinical criteria for human RPE, having at least two of the following: worsening dyspnoea, hypoxaemia, tachypnoea, hemodynamic instability, or a new cough lasting more than 20 min (Feller-Kopman *et al.* 2007). The presence of diffuse bilateral pulmonary oedema was confirmed by the rapid development, and subsequent rapid resolution, of audible inspiratory crackles and multiple ultrasonographic ring-down artefacts present across the entire lungfields. Ultrasonographic ring-down artefact score is correlated with extravascular lung water content, and is sufficiently sensitive to detect pulmonary interstitial oedema even before it becomes clinically apparent (Jambrik *et al.* 2004; Agricola *et al.* 2005). Given the utility of ultrasonography for diagnosis of pulmonary oedema (Louvet and Bourgeois 2008), thoracic radiography and endoscopy were not considered necessary to confirm the presence of pulmonary oedema, and would likely have caused the

horse further distress. Clinical examination and ultrasonography ruled out other potential causes of acute deterioration following attempted thoracic drainage including iatrogenic injury to lungs, heart, diaphragm and abdominal viscera, pneumothorax, haemothorax, and cardiac dysrhythmia. While an adverse reaction to tPA cannot he excluded, this appears unlikely given that subsequent instillation of similar doses of tPA into both pleural cavities on three occasions had no apparent adverse effect. While thoracocentesis and intrapleural instillation of tPA can exacerbate pleurodynia in human patients, increased pleurodynia alone was unlikely to have caused the clinical deterioration, since administration of morphine and meloxicam resulted in only a minor improvement in clinical parameters. More likely, as occurs in human RPE (Feller-Kopman 2007), increased pleurodynia was a symptom of RPE, possibly due to the increased rate and depth of breathing occurring in response to hypoxaemia.

As occurred in this case, clinical signs of RPE in human patients typically commence within 1-2 h after intervention, and always within 24 h (Mahfood *et al.* 1988; Genofre *et al.* 2003; Taira *et al.* 2014). Careful patient monitoring is important during this critical time period, because early recognition and fast symptom-orientated treatment are necessary for survival (Taira *et al.* 2014). Treatment of symptomatic human RPE is largely supportive, including diuresis, supplemental oxygen, positive pressure ventilation, morphine and glucocorticoids (Light 1995; Taira *et al.* 2014). The mare in this report received a diuretic, supplemental oxygen and morphine. Intravenous crystalloid therapy was discontinued because volume overload may exacerbate pulmonary oedema and increase patient mortality, particularly when pulmonary vascular permeability is increased (Calfee and Matthay 2007; Lyons 2008). Hydroxyethyl starch was administered because it can attenuate pulmonary vascular permeability and improve haemodynamics and cardiac output without worsening pulmonary oedema and pulmonary mechanics in human acute respiratory distress syndrome (Huang *et al.* 2009). While morphine was administered largely for its analgesic properties, it can aid treatment of human cardiogenic

pulmonary oedema by reducing anxiety, improving breathing pattern and reducing venous tone and peripheral vascular resistance via central sympatholysis (Robin *et al.* 1973). Other reported treatments for pulmonary oedema not used in this case include acepromazine, inhaled β_2-agonist bronchodilators, inhaled frusemide, nebulization of 20% alcohol to reduce surface tension of oedema fluid and foam formation, and suction of accumulated fluid from proximal airways (Atabai *et al.* 2002; Senior 2005; Dunkel 2006). Recommended protocols to minimise occurrence of human RPE include use of small-diameter thoracic drains and avoidance of suction pressures exceeding 10-20 cmH_2O, although adherence to these protocols does not eliminate the risk of RPE (Light 1995; Feller-Kopman *et al.* 2007; Taira *et al.* 2014).

In summary, this case suggests that RPE can occur as an iatrogenic complication of rapid lung re-expansion following intrapleural tPA administration in horses with fibrinous pleural effusion. Clinicians should consider this complication when a horse undergoing this treatment has sudden worsening of dyspnoea, hypoxaemia, tachypnoea, hemodynamic instability and/or sudden onset coughing.

Figures

Figure 1; Pleural fluid collected at 48 h after tPA instillation, showing numerous clumps of fibrin consistent with pleural fibrinolysis.

Figure 2; Close up view of fibrin clump.

Supplementary Video Files

Video 1; Ultrasonogram of the left ventral hemithorax recorded on Day 2 of hospitalisation showing organising fibrinous pleuropneumonia. The extensive fibrinous pleural loculations and inter-pleural adhesions are restricting lung expansion, and consequently there is little

movement of the lung in relation to the parietal pleura. There is also marked collapse of the ventral lung. Dorsal to left of image. Scale = cm.

Video 2; Thoracic ultrasonogram from a horse with cardiogenic pulmonary oedema illustrating multiple ring-down artefacts, similar to those identified in the case reported herein. Please note that this image is included for illustrative purposes only and is not from the subject of this case report. Dorsal to left of image. Scale = cm.

Video 3; Ultrasonogram of the left ventral hemithorax recorded 18 h after tPA instillation. There is clear evidence of pleural fibrinolysis, with a marked reduction in fibrin loculations and an accompanying increase in freely moving fluid containing hyperechoic foci. The pericardio-diaphragmatic ligament is now evident. The previously restricted and adherent lung is now moving more freely in relation to the parietal pleura during the breath cycle. There is also marked reduction in the volume of collapsed lung indicating pulmonary re-inflation. Dorsal to left of image. Scale = cm.

References

Agricola, E., Bove, T., Oppizzi, M., Marino, G., Zangrillo, A., Margonato, A. and Picano E. (2005) Ultrasound comet-tail images: a marker of pulmonary edema. *Chest* **127,** 1690-1695.

Atabai, K., Ware, L.B., Snider, M.E., Koch, P., Daniel, B., Nuckton, T.J. and Matthay M.A. (2002) Aerosolized β2-adrenergic agonists achieve therapeutic levels in the pulmonary edema fluid of ventilated patients with acute respiratory failure. *Intens. Care Med.* **28**, 705-711.

Ball, M.A. and Trim, C.M. (1996) Post anaesthetic pulmonary oedema in two horses. *Eq. vet. Educ.* **8,** 13-16.

Calfee, C.S. and Matthay, M.A. (2007) Nonventilatory treatments for acute lung injury and ARDS. *Chest* **131**, 913-920.

Dunkel, B. (2006) Acute lung injury and acute respiratory distress syndrome in foals. *Clin. Tech. Equine Pract.* **5**, 127-133.

Feller-Kopman, D., Berkowitz, D., Boiselle, P. and Ernst, A. (2007) Large-volume thoracentesis and the risk of reexpansion pulmonary edema. *Ann. Thorac. Surg.* **84,** 1656-1661.

Genofre, E.H., Vargas, F.S., Lisete, R., Teixeira, L.R., Costa Vaz, M.A. and Marchi, E. (2003) Reexpansion pulmonary edema. *J. Pneumol.* **29**, 101-106.

Huang, C.C., Kao, K.C., Hsu, K.H., Ko, H.W., Li, L.F., Hsieh, M.J. and Tsai, Y.H. (2009) Effects of hydroxyethyl starch resuscitation on extravascular lung water and pulmonary permeability in sepsis-related acute respiratory distress syndrome. *Crit. Care Med.* **37**, 1948-1955.

Jambrik, Z., Monti, S., Coppola, V., Agricola, E., Mottola, G., Miniati, M. and Picano, E. (2004) Usefulness of ultrasound lung comets as a nonradiologic sign of extravascular lung water. *Am. J. Cardiol.* **93**, 1265-1270.

Kaartinen, M.J., Pang, D.S.J. and Cuvelliez, S.G. (2010) Post-anesthetic pulmonary edema in two horses. *Vet. Anaes. Analg.* **37,** 136-143.

Kim, Y.K., Kim, H., Lee, C.C., Choi, H.J., Lee, K.H., Hwang, S.O., Oh, J.H., Lee, Y.H.L. and Singer, A.J. (2009) New classification and clinical characteristics of re-expansion pulmonary oedema after treatment of spontaneous pneumothorax. *Am. J. Emerg. Med.* **27**, 961-967.

Light, R.W.: Pleural Diseases. Retford D (ed). Baltimore, Williams & Wilkins Co, 3rd Ed, 1995, pp 268-269.

Louvet, A. and Bourgeois, J.M. (2008) Lung ring-down artefact as a sign of pulmonary alveolar-interstitial disease. *Vet. Radiol. Ultrasound* **49**, 374-377.

Lyons, W.S. (2008) Nonventilatory treatments for ARDS? Future directions. *Chest* **133**, 586-587.

Mahfood, S., Hix, W.R., Aaron, B.L., Blaes, P. and Watson, D.C. (1988) Reexpansion pulmonary edema. *Ann. Thorac. Surg.* **45**, 340-345.

Robin, E.D., Cross, C.E. and Zelis, R. (1973) Pulmonary edema. 2. *N. Engl. J. Med.* **288**, 292-304.

Senior, M. (2005) Post-anaesthetic pulmonary oedema in horses: a review. *Vet. Anaes. Analg.* **32**, 190-200.

Sherman, S.C. (2003) Reexpansion pulmonary edema: a case report and review of the current literature. *J. Emerg. Med.* **24**, 23-27.

Sohara, Y. (2008) Reexpansion pulmonary oedema. Ann. Thorac. Cardiovasc. Surg. **14**, 205-209.

Taira, N., Kawabata, T., Ichi, T., Yohena, T., Kawasaki, H. and Ishikawa K. (2014) An analysis of and new risk factors for reexpansion pulmonary edema following spontaneous pneumothorax. *J. Thorac. Dis.* **6**, 1187-1192.

Tomlinson, J.E., Byrne, E., Pusterla, N., Magdesian, K.G., Hilton, H.G., McGorum, B., Davis, E., Schoster, A., Arroyo, L., Dunkel, B., Carslake, H., Boston, R.C. and Johnson A.L. (2015) The use of recombinant tissue plasminogen activator (rTPA) in the treatment of fibrinous pleuropneumonia in the horse: 25 cases (2007-2012). *J. Vet. Intern. Med.* **29**, 1403-1409.